Comment apprécier et suivre la MRC chez l’enfant et le sujet âgé?

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Université de Liège
CHU Sart Tilman
BELGIQUE

LIÈGE université

- 70 = septante
- 90 = nonante

- Comment estimer?

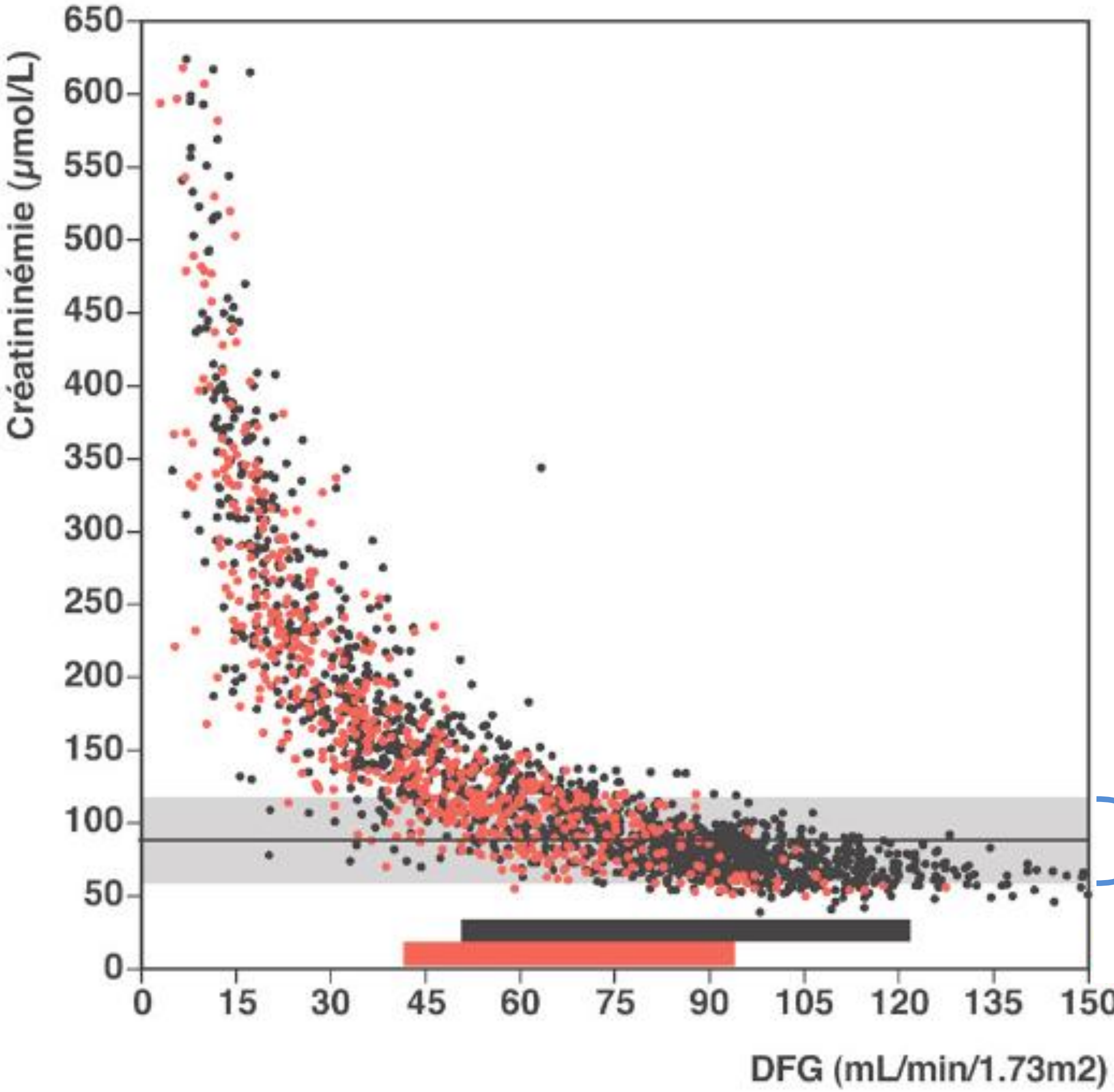
- Comment mesurer?

- Comment estimer?
- Comment mesurer?

Serum creatinine

- Très prescrit
- …mais le plus important est d'en connaitre les limitations
- Limitations physiologiques
- Limitations analytiques
- Limitations "mathématiques"

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531



Cohorte NephroTest (France)
Quel DFG correspond à une concentration de créatinine mesurée à 0.9 mg/dL (80 µmol/L) ?

IC 95% pour sujets <65 ans
IC 95% pour sujets >65 ans

Valeurs normales de créatinine

Avec la permission de Marc Froissart

Mesure de la créatinine sérique
Limitations analytiques

- Méthodes de Jaffe
- Méthodes enzymatiques
- Différentes méthodes mais aussi différents « assays »
- Interférences

Amélioration significative dans la standardisation (IDMS traceable)

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Limitations physiologiques

- Production extra-rénale

- Sécrétion tubulaire de créatinine

10 to 40%

Sécrétion augmente alors que DFG diminue

Non prédictible à l'échelon individuel

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Limitations physiologiques

- Production (relativement) constante d'origine musculaire => la concentration de créatinine dépend de la masse musculaire, pas seulement du DFG
    - genre
    - âge
    - ethnicité
    - Masse musculaire

Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Creatinine: à la poubelle?

- Bon marché! (0.04€ /Jaffe)
- Bonne spécificité
- Bon CV analytique
- Préférence pour les méthodes enzymatiques

Clairance de créatinine

- N'est recommandée par aucun guidelines
- Sécrétion tubulaire
- Manque de précision:

erreurs dans la collecte

22 à 27% chez les patients « entrainés »
50 to 70 % pour les autres (enfants…)

importante variabilité intra-individuelle de l'excrétion urinaire de créatinine

KDIGO, Kidney Int, 2012, 3
Perrone RD, Clin Chem, 1992, 38, 1933
Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531

Equations les plus utilisées

ADULTES

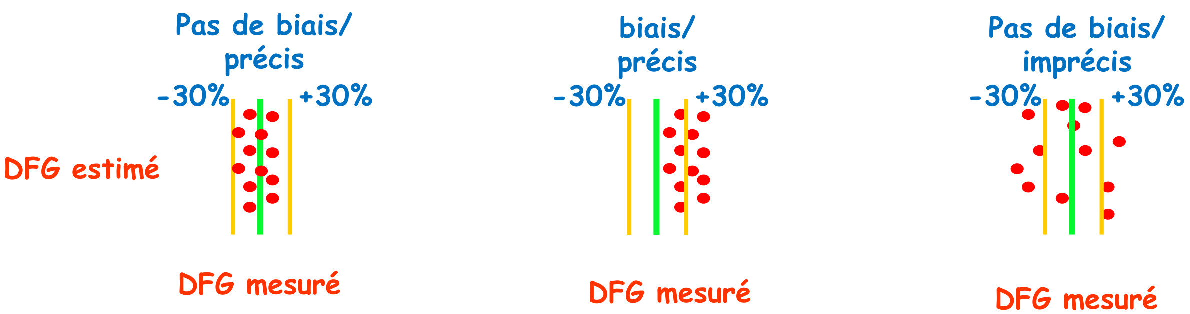
- (Cockcroft)
- MDRD
- CKD-EPI

ENFANTS

- Schwartz
- Schwartz-Lyon

Statistiques

- Corrélation: une condition “*sine qua non”* mais insuffisante!
- Biais: différence moyenne entre 2 valeurs = erreur systématique
- Précision: SD autour de ce biais = erreur aléatoire
- Exactitude 30% = % du DFG estimée dans ± 30% du DFG mesuré



Bland JM, Altman DG, Lancet, 1986, 8476, 307
Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396

MDRD versus CKD-EPI

4-Variable MDRD study equation (IDMS traceable)

GFR (ml/min/1.73 m^2) =
$175 \times$ SCr (mg/dl)$^{-1.154} \times$ age$^{-0.203} \times 0.742$ (if woman)
(same ethnicity correction factors)

Table 2. **The CKD-EPI Equation for Estimating GFR on the Natural Scale***

Race and Sex	Serum Creatinine Level, *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Levey AS, Ann Intern Med, 1999, p461
Levey AS, Ann Intern Med, 2009 p604

Equation CKD-EPI

ARTICLE

Annals of Internal Medicine

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, MD, PhD, MHS, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)*

Ann Intern Med. 2009;150:604-612.

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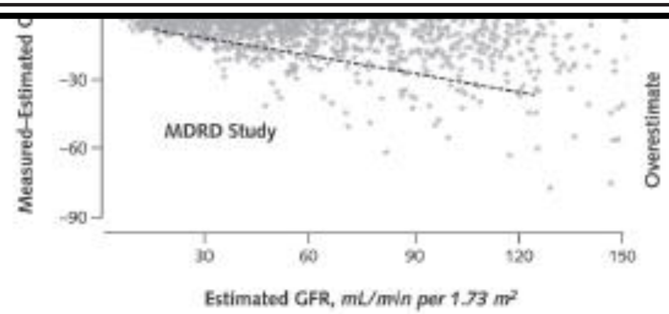
- CKD-EPI
- “Development dataset”: n=5504
- “Internal validation”: n=2750
- “External validation”: n=3896
- Créatinine calibrée
- DFG médian = 68 mL/min/1.73 m^2

Figure. Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.

Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

Variable and Equation	All Patients	Patients With Estimated GFR <60 mL/min per 1.73 m²	Patients With Estimated GFR ≥60 mL/min per 1.73 m²
Median difference (95% CI), *mL/min per 1.73 m²*†			
CKD-EPI	2.5 (2.1–2.9)	2.1 (1.7–2.4)	3.5 (2.6–4.5)
MDRD Study	5.5 (5.0–5.9)	3.4 (2.9–4.0)	10.6 (9.8–11.3)
Interquartile range for differences (95% CI), *mL/min per 1.73 m²*‡			
CKD-EPI	16.6 (15.9–17.3)	11.3 (10.7–12.1)	24.2 (22.8–25.3)
MDRD Study	18.3 (17.4–19.3)	12.9 (12.0–13.6)	25.7 (24.4–27.1)
P_{30} (95% CI), %§			
CKD-EPI	84.1 (83.0–85.3)	79.9 (78.1–81.7)	88.3 (86.9–89.7)
MDRD Study	80.6 (79.5–82.0)	77.2 (75.5–79.0)	84.7 (83.0–86.3)
Root mean square error (95% CI)			
CKD-EPI	0.250 (0.241–0.259)	0.284 (0.270–0.298)	0.213 (0.203–0.223)
MDRD Study	0.274 (0.265–0.283)	0.294 (0.280–0.308)	0.248 (0.238–0.258)



Discussion:
MDRD or CKD-EPI ?

- Prévalence plus basse de la MDRD dans les études épidémiologiques
- Meilleure prédiction CV => meilleures à l'échelle population
- Meilleur biais pour les DFG >60 (90?) ml/min/1.73m^2 mais précision pas meilleure => réellement meilleur à l'échelle individuelle?

Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396
Delanaye P, Nephrol Ther, 2012, 8, 199

Le prix à payer?

Relative Performance of the MDRD and CKD-EPI Equations for Estimating Glomerular Filtration Rate among Patients with Varied Clinical Presentations

Kazunori Murata, Nikola A. Baumann,* Amy K. Saenger,* Timothy S. Larson,*† Andrew D. Rule,†‡ and John C. Lieske*†*

*Department of Laboratory Medicine and Pathology, †Department of Internal Medicine, Division of Nephrology and Hypertension, and ‡Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, Minnesota

Correspondence: Dr. John C. Lieske, Mayo Clinic Division of Nephrology and Hypertension, 200 First Street SW, Rochester, MN 55905. Phone: 507-266-7960; Fax: 507-266-7891; E-mail: Lieske.John@mayo.edu

Summary

Background The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed using both CKD and non-CKD patients to potentially replace the Modification of Diet in Renal Disease (MDRD) equation that was derived with only CKD patients. The objective of our study was to compare the accuracy of the MDRD and CKD-EPI equations for estimating GFR in a large group of patients having GFR measurements for diverse clinical indications.

Design, setting, participants, and measurements A cross-sectional study was conducted of patients who underwent renal function assessment for clinical purposes by simultaneous measurements of serum creatinine and estimation of GFR using the MDRD and CKD-EPI equations and renal clearance of iothalamate (n = 5238).

Results Bias compared with measured GFR (mGFR) varied for each equation depending on clinical presentation. The CKD-EPI equation demonstrated less bias than the MDRD equation in potential kidney donors (−8% *versus* −18%) and postnephrectomy donors (−7% *versus* −15%). However, the CKD-EPI equation was slightly more biased than the MDRD equation in native CKD patients (6% *versus* 3%), kidney recipients (8% *versus* 1%), and other organ recipients (9% *versus* 3%). Among potential kidney donors, the CKD-EPI equation had higher specificity than the MDRD equation for detecting an mGFR <60 ml/min per 1.73 m^2 (98% *versus* 94%) but lower sensitivity (50% *versus* 70%).

Conclusions Clinical presentation influences the estimation of GFR from serum creatinine, and neither the CKD-EPI nor MDRD equation account for this. Use of the CKD-EPI equation misclassifies fewer low-risk patients as having reduced mGFR, although it is also less sensitive for detecting mGFR below specific threshold values used to define CKD stages.

Clin J Am Soc Nephrol 6: 1963–1972, 2011. doi: 10.2215/CJN.02300311

Le prix à payer?

- Quel serait votre choix?

Mieux estimer le DFG d'un *<u>sujet</u>* avec une DFG mesuré entre 90 et 120 mL/min/1.73 m²?

Mieux estimer le DFG d'un *<u>patient</u>* avec un DFG mesuré entre 30 et 60 mL/min/1.73 m²?

(provocation!)

Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396
Delanaye P, Nephrol Ther, 2012, 8, 199

Pédiatrie: The Schwartz équation

- Original Schwartz, 1976 (n=186 +77)

$$eGFR = k \times L\ (cm)/P_{Cr}\ (mg/dL)$$

where $k \sim 0.33$ (preterm infant), $k \sim 0.45$ (full term), $k \sim 0.55$ (children and adolescent females), $k \sim 0.7$ (adolescent males)

- Updated Schwartz, 2009, (n=349) P30=79,4%

$eGFR = 0.413 \times L\ (cm)/P_{Cr}\ (mg/dL)$ (0,34 for full term, 0,25 for preterm)

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

Schwartz GJ, Pediatrics, 1976, 58, 259
Schwartz GJ, J Am Soc Nephrol, 2009, 20, 629

Schwartz-Lyon (n=1054)

- Adolescent de + 13 ans k=0,413
- Adolescent de – 13 ans et adolescentes k=0,368
- K = variable selon les centres (DFG, créatinine)

Table 2. Mean bias and accuracies according to age groups and equations

Group	CG	MDRD	CKD-EPI	Schwartz 2009	Schwartz-Lyon
Group 1 (10–12 yr) (*n*=225)					
mGFR=93.4±29.3					
eGFR	150.9±45.2	179.3±59.0	144.6±25.6	98.6±25.6	88.7±25.0
correlation coefficient (*r*)	0.87	0.84	0.84	0.88	0.89
mean ratio (eGFR/mGFR)	1.65±0.32	1.95±0.42	1.65±0.39	1.10±0.21	0.98±0.18
95% limits of agreement	1.02, 2.28	1.13, 2.77	0.89, 2.41	0.69, 1.51	0.63, 1.33
10% accuracy	1	1	3	47[a]	48[a]
30% accuracy	10	4	17	86	92[b]
Group 2 (13–17 yr) (*n*=322)					
mGFR=87.3±32.5					
eGFR	127.1±45.4	125.3±50.9	119.9±32.5	87.2±28.3	85.7±29.7
correlation coefficient (*r*)	0.88	0.86	0.85	0.89	0.89
mean ratio (eGFR/mGFR)	1.50±0.33	1.46±0.37	1.44±0.32	1.04±0.21	1.01±0.20
95% limits of agreement	0.85, 2.15	0.74, 2.18	0.81, 2.07	0.63, 1.45	0.62, 1.40
10% accuracy	6	14	10	41[a]	37[a]
30% accuracy	31	41	38	88	90
Group 3 (18–21 yr) (*n*=262)					
mGFR=90.4±30.1					
eGFR	113.2±39.3	102.9±40.1	106.9±30.5	82.0±26.4	79.4±27.3
correlation coefficient (*r*)	0.85	0.85	0.86	0.86	0.85
mean ratio (eGFR/mGFR)	1.28±0.29	1.16±0.30	1.23±0.27	0.94±0.22	0.90±0.41
95% limits of agreement	0.71, 1.85	0.57, 1.75	0.96, 1.56	0.51, 1.37	0.49, 1.31
10% accuracy	25	36	27	32	28
30% accuracy	59	75	69	84[a]	83[a]
Group 4 (22–25 yr) (*n*=245)					
mGFR=84.1±30.3					
eGFR	102.5±35.5	89.3±31.8	97.3±28.4	76.0±25.7	73.0±25.2
correlation coefficient (*r*)	0.85	0.85	0.86	0.86	0.85
mean ratio (eGFR/mGFR)	1.27±0.31	1.10±0.27	1.21±0.28	0.94±0.21	0.90±0.23
95% limits of agreement	0.66, 1.87	0.57, 1.63	0.66, 1.76	0.53, 1.35	0.45, 1.35
10% accuracy	29	36	33	33	31
30% accuracy	64	78	72	85	82

De Souza VS, Plos One, 2012, 7, e53439
Selistre L, J Am Soc Nephrol, 2012, 23, 989

PLOS | MEDICINE

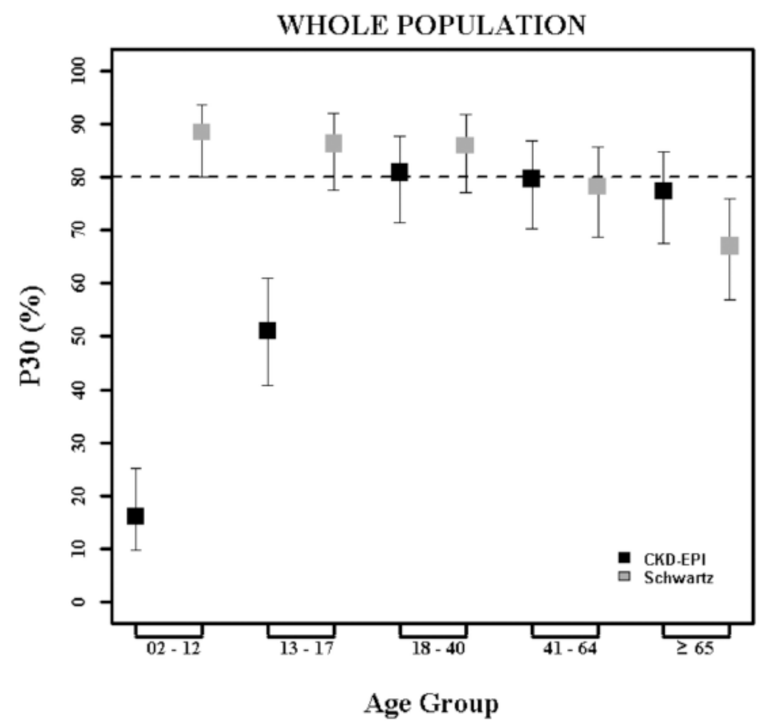
PLoS Med 13(3): e1001979. doi:10.1371/journal.pmed.1001979

RESEARCH ARTICLE

Comparison of the Schwartz and CKD-EPI Equations for Estimating Glomerular Filtration Rate in Children, Adolescents, and Adults: A Retrospective Cross-Sectional Study

Luciano Selistre[1,2,3,4,5]*, Muriel Rabilloud[5,6,7], Pierre Cochat[6,7,8,9], Vandréa de Souza[1,2,4], Jean Iwaz[5,6,7], Sandrine Lemoine[1,8,10], Françoise Beyerle[1,11], Carlos E. Poli-de-Figueiredo[3], Laurence Dubourg[1,6,8]

- N=10,610
- Inuline
- Schwartz



Retour chez adulte
MDRD – CKD-EPI: What else?

- Equation Bis

- Equation Lund-Malmö

- Equation FAS

- Autre biomarqueurs: cystatine C

Annals of Internal Medicine | Original Research

Two Novel Equations to Estimate Kidney Function in Persons Aged 70 Years or Older

Elke S. Schaeffner, MD, MS*; Natalie Ebert, MD, MPH*; Pierre Delanaye, MD, PhD; Ulrich Frei, MD; Jens Gaedeke, MD; Olga Jakob; Martin K. Kuhlmann, MD; Mirjam Schuchardt, PhD; Markus Tölle, MD; Reinhard Ziebig, PhD; Markus van der Giet, MD; and Peter Martus, PhD

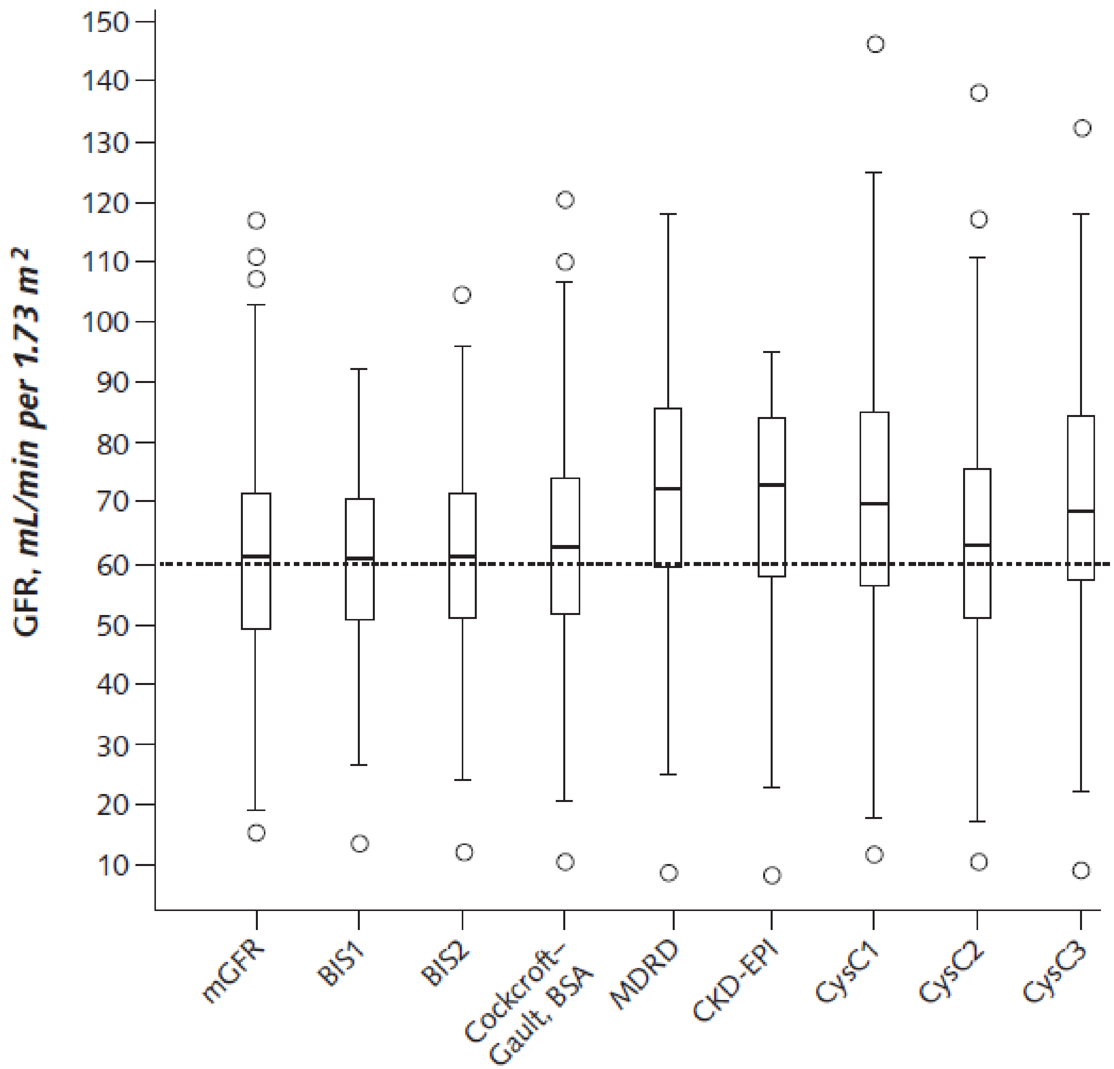
BIS1:

$$3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82 \text{ (if female)}$$

- n=610, iohexol, créatinine enzymatiques calibrée
- DFG moyen = 52 mL/min/1,73 m²

Ann Intern Med. 2012;157:471-481

Figure 1. **Comparison of mGFR with eGFR equations in the validation sample.**



Boxes indicate medians (*line inside box*), quartiles (*upper and lower margins of box*). Antennae are defined by the rule upper–lower box margin ± 1.5 × interquartile range. Circles indicate outliers.

Ulf Nyman*, Anders Grubb, Anders Larsson, Lars-Olof Hansson, Mats Flodin, Gunnar Nordin, Veronica Lindström and Jonas Björk

The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population

Clin Chem Lab Med 2014, 52(6), 815-824

Revised Lund-Malmö Study equation (LM Revised) [34]

$e^{X-0.0158\times Age+0.438\times \ln(Age)}$

Female	pCr<150 µmol/L:	$X=2.50+0.0121\times(150-pCr)$
Female	pCr≥150 µmol/L:	$X=2.50-0.926\times\ln(pCr/150)$
Male	pCr<180 µmol/L:	$X=2.56+0.00968\times(180-pCr)$
Male	pCr≥180 µmol/L:	$X=2.56-0.926\times\ln(pCr/180)$

- Lund-Malmo
- n=3495 (chez 2847 sujets), iohexol, créatinine calibrée
- DFG moyen = 60 mL/min/1,73 m²

Nephrol Dial Transplant (2016) 31: 798–806
doi: 10.1093/ndt/gfv454
Advance Access publication 29 February 2016

An estimated glomerular filtration rate equation for the full age spectrum

Hans Pottel[1], Liesbeth Hoste[1], Laurence Dubourg[2], Natalie Ebert[3], Elke Schaeffner[3], Bjørn Odvar Eriksen[4], Toralf Melsom[4], Edmund J. Lamb[5], Andrew D. Rule[6], Stephen T. Turner[6], Richard J. Glassock[7], Vandréa De Souza[8], Luciano Selistre[9], Christophe Mariat[10], Frank Martens[11] and Pierre Delanaye[12]

Example 1: A healthy 18-year-old male with a body height (L) of 180 cm and SCr of 0.90 mg/dL:

Paediatric equation (Schwartz): $eGFR = 0.413 \times L/SCr = 0.413 \times 180/0.90 = 83$ mL/min/1.73 m^2.

Adult equation (CKD-EPI): $eGFR = 141 \times (0.90/0.90)^{-1.209}$ $0.993^{18} = 124$ mL/min/1.73 m^2. **+50%**

N=6870, 735 enfants

Table 1. ***Q*-values [=median serum creatinine in µmol/L (mg/dL)] for the FAS equation, according to age or height (from refs [4, 5, 10])**

Age, years	Height[a], cm	Q[b], µmol/L (mg/dL)
Boys and girls		
1	75.0	23 (0.26)
2	87.0	26 (0.29)
3	95.5	27 (0.31)

$$eGFR = 107.3/(Scr/Q),$$
$$Q = 0.21 + 0.057 \times Age - 0.0075 \times Age^2 + 0.00064 \times Age^3 - 0.000016 \times Age^4 \text{ for boys}$$
$$Q = 0.23 + 0.034 \times Age - 0.0018 \times Age^2 + 0.00017 \times Age^3 - 0.0000051 \times Age^4 \text{ for girls}$$
$$eGFR = 107.3/(Scr/Q),$$
$$Q = 3.94 - 13.4 \times L + 17.6 \times L^2 - 9.84 \times L^3 + 2.04 \times L^4 \text{ for boys and girls}$$

Age, years	Height[a], cm	Q[b], µmol/L (mg/dL)
12	152.5	50 (0.57)
13	159.0	52 (0.59)
14	165.0	54 (0.61)
Male adolescents		
15	172.0	64 (0.72)
16	176.0	69 (0.78)
17	178.0	72 (0.82)
18	179.0	75 (0.85)
19	180.0	78 (0.88)
Male adults		
≥20	≥181.5	80 (0.90)
Female adolescents		
15	164.5	57 (0.64)
16	166.0	59 (0.67)
17	166.5	61 (0.69)
18	167.0	61 (0.69)
19	167.5	62 (0.70)
Female adults		
≥20	≥168.0	62 (0.70)

[a]Height is the median height of a child or adolescent at the specified age (Belgian growth curves).

Table 3. Prediction performance results of different eGFR equations on the pooled databases according to age group and measured GFR categories (mGFR below or above 60 mL/min/1.73 m^2)

Pooled data	eGFR equivalent	RMSE (95% CI)	Constant bias (95% CI)	Proportional bias (95% CI)	P10, % (95% CI)	P30, % (95% CI)
Children and adolescents <18 years						
All (n = 735)	FAS	20.1 (18.5, 21.6)	−1.7 (−3.1, −0.2)*,†	1.01 (0.99, 1.03)*,†	40.1 (36.6, 43.7)	87.5 (85.1, 89.9)*
mGFR = 94.5	FAS-height	19.8 (18.1, 21.4)	−2.7 (−4.1, −1.3)*,‡	1.00 (0.98, 1.01)*,‡	41.9 (38.3, 45.5)	88.8 (86.6, 91.1)†
	Schwartz	21.7 (19.5, 23.7)	6.0 (4.5, 7.5)†,‡	1.09 (1.07, 1.11)†,‡	40.1 (36.6, 43.7)	83.8 (81.1, 86.5)*,†
mGFR < 60 (n = 99)	FAS	14.6 (8.5, 18.9)	6.2 (3.6, 8.9)*,†	1.15 (1.09, 1.21)*,†	34.3 (24.8, 43.9)	75.8 (67.2, 84.3)
mGFR = 45.1	FAS-height	13.5 (4.2, 18.6)	4.7 (2.2, 7.2)*,‡	1.12 (1.06, 1.17)*,‡	39.4 (25.6, 49.2)	77.8 (69.4, 86.1)*
	Schwartz	16.7 (8.2, 22.1)	9.4 (6.7, 12.2)†,‡	1.22 (1.16, 1.28)†,‡	31.3 (22.0, 40.6)	70.7 (61.6, 79.8)*
mGFR ≥ 60 (n = 636)	FAS	20.8 (19.1, 22.4)	−2.9 (−4.5, −1.3)*,†	0.99 (0.97, 1.00)*,†	41.0 (37.2, 44.9)	89.3 (86.9, 91.7)*
mGFR = 102.2	FAS-height	20.6 (18.9, 22.3)	−3.8 (−5.4, −2.3)*,‡	0.98 (0.96, 0.99)*,‡	42.3 (38.4, 46.1)	90.6 (88.3, 92.8)†
	Schwartz	22.4 (20.0, 24.5)	5.4 (3.7, 7.1)†,‡	1.07 (1.05, 1.09)†,‡	41.5 (37.7, 45.3)	85.8 (83.1, 88.6)*,†
Adults 18–70 years						
All (n = 4371)	FAS	17.2 (16.6, 17.8)	5.0 (4.5, 5.5)*	1.12 (1.11, 1.12)*	40.4 (38.9, 41.9)*	81.6 (80.4, 82.7)
mGFR = 78.6	CKD-EPI	16.4 (15.8, 16.9)	6.3 (5.9, 6.8)*	1.13 (1.12, 1.14)*	42.5 (41.1, 44.0)*	81.9 (80.7, 83.0)
mGFR < 60 (n = 1089)	FAS	19.0 (17.7, 20.2)	13.4 (12.6, 14.2)*	1.35 (1.33, 1.37)*	19.1 (16.8, 21.4)*	52.2 (49.3, 55.2)*
mGFR = 42.3	CKD-EPI	19.2 (18.1, 20.3)	12.7 (11.8, 13.5)*	1.31 (1.29, 1.34)*	21.9 (19.4, 24.3)*	55.2 (52.2, 58.1)*
mGFR ≥ 60 (n = 3282)	FAS	16.6 (15.9, 17.2)*	2.2 (1.6, 2.7)*	1.04 (1.03, 1.04)*	47.5 (45.8, 49.2)*	91.3 (90.3, 92.3)
mGFR = 90.6	CKD-EPI	15.3 (14.7, 15.8)*	4.2 (3.7, 4.7)*	1.07 (1.06, 1.07)*	49.4 (47.7, 51.1)*	90.7 (89.7, 91.7)
Older adults ≥70 years						
All (n = 1764)	FAS	11.2 (10.7, 11.7)*	−1.1 (−1.6, −0.6)*	1.02 (1.01, 1.03)*	39.7 (37.5, 42.0)*	86.1 (84.4, 87.7)*
mGFR = 55.6	CKD-EPI	12.9 (12.4, 13.4)*	5.6 (5.1, 6.2)*	1.13 (1.12, 1.15)*	35.0 (32.8, 37.3)*	77.6 (75.7, 79.6)*
	BIS1[a]	12.0 (11.4, 12.6)	−1.2 (−1.9, −0.6)	1.05 (1.03, 1.07)	34.7 (32.0, 37.4)	81.8 (79.7, 84.0)
mGFR < 60 (n = 986)	FAS	9.5 (8.8, 10.1)*	2.2 (1.6, 2.7)*	1.09 (1.07, 1.11)*	36.6 (33.6, 39.6)*	81.0 (78.6, 83.5)*
mGFR = 40.7	CKD-EPI	13.1 (12.3, 13.8)*	6.9 (6.2, 7.6)*	1.19 (1.17, 1.21)*	29.5 (26.7, 32.4)*	67.7 (64.8, 70.7)*
	BIS1[a]	9.7 (9.0, 10.3)	3.7 (3.0, 4.4)	1.16 (1.13, 1.18)	35.3 (31.8, 38.8)	75.4 (72.2, 78.5)
mGFR ≥ 60 (n = 778)	FAS	13.1 (12.3, 13.8)	−5.2 (−6.1, −4.4)*	0.94 (0.93, 0.95)*	43.7 (40.2, 47.2)	92.4 (90.6, 94.3)
mGFR = 74.4	CKD-EPI	12.7 (12.1, 13.3)	4.1 (3.2, 4.9)*	1.07 (1.06, 1.08)*	42.0 (38.6, 45.5)	90.1 (88.0, 92.2)
	BIS1[a]	14.8 (13.7, 15.7)	−8.6 (−9.7, −7.5)	0.90 (0.88, 0.91)	33.9 (29.6, 38.1)	91.5 (89.0, 94.0)

The same symbols (*,†,‡) within each subgroup and column indicate significant differences (paired t-test for constant and proportional bias, McNemar's test for P10 and P30 = % of subjects with an eGFR value within 10% and 30% of measured GFR).

[a]For the BIS1 performance results, the data (n= 570) from the BIS1 study were not included (therefore, no comparisons with FAS and CKD-EPI were made).

Pottel H, Nephrol Dial Transplant, 2016, 31, 798

Hoste L, Nephrol Dial Transplant, 2014, 29, 1082

Cystatine C

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ORIGINAL ARTICLE

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

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Table 1. Characteristics of Study Participants, According to Data Set.*

Characteristic	Development and Internal Validation (N = 5352)	External Validation (N = 1119)	P Value
Age — yr	47±15	50±17	<0.001
Age group — no. (%)			
<40 yr	2008 (38)	357 (32)	<0.001
40–65 yr	2625 (49)	530 (47)	
>65 yr	719 (13)	232 (21)	
Male sex — no. (%)	3107 (58)	663 (59)	0.46
Black race — no. (%)†	2123 (40)	30 (3)	<0.001
Diabetes — no. (%)	1726 (32)	594 (53)	<0.001
Body-mass index‡			
Mean	28±6	25±4	<0.001
<20 — no. (%)	214 (4)	81 (7)	<0.001
20–24 — no. (%)	1585 (30)	503 (45)	
25–30 — no. (%)	1881 (35)	386 (35)	
>30 — no. (%)	1671 (31)	149 (13)	
Mean weight — kg	83±20	74±15	<0.001
Mean height — cm	171±10	170±9	0.017
Mean body-surface area — m^2	1.94±0.24	1.85±0.21	<0.001
Mean serum cystatin C — ml/liter	1.4±0.7	1.5±0.8	0.01
Mean serum creatinine — mg/dl§	1.6±0.9	1.6±1.1	0.15
Mean measured GFR — ml/min/1.73 m^2 of body-surface area	68±39	70±41	0.13
Measured GFR — no. (%)			
<15 ml/min/1.73 m^2	160 (3)	51 (5)	<0.001
15–29 ml/min/1.73 m^2	785 (15)	166 (15)	
30–59 ml/min/1.73 m^2	1765 (33)	316 (28)	
60–89 ml/min/1.73 m^2	1105 (21)	215 (19)	
90–119 ml/min/1.73 m^2	862 (16)	199 (18)	
>120 ml/min/1.73 m^2	675 (13)	172 (15)	

Table 2. Creatinine Equation (CKD-EPI 2009), Cystatin C Equation (CKD-EPI 2012), and Creatinine–Cystatin C Equation (CKD-EPI 2012) for Estimating GFR, Expressed for Specified Sex, Serum Creatinine Level, and Serum Cystatin C Level.*

Basis of Equation and Sex	Serum Creatinine†	Serum Cystatin C	Equation for Estimating GFR
	mg/dl	*mg/liter*	
CKD-EPI creatinine equation‡			
Female	≤0.7		$144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$ [× 1.159 if black]
Female	>0.7		$144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
Male	≤0.9		$141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$ [× 1.159 if black]
Male	>0.9		$141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
CKD-EPI cystatin C equation§			
Female or male		≤0.8	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age}$ [× 0.932 if female]
Female or male		>0.8	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age}$ [× 0.932 if female]
CKD-EPI creatinine–cystatin C equation¶			
Female	≤0.7	≤0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Female	>0.7	≤0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Male	≤0.9	≤0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Male	>0.9	≤0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]

Table 3. Use of the CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012), and CKD-EPI Creatinine–Cystatin C Equations (2012) in the External-Validation Data Set Comprising 1119 Participants.*

Variable	Estimated GFR			
	Overall	<60	60–89	≥90
	ml/min/1.73 m^2 of body-surface area			
Bias — median difference (95% CI)				
Creatinine equation	3.7 (2.8 to 4.6)	1.8 (1.1 to 2.5)	6.6 (3.5 to 9.2)	11.1 (8.0 to 12.5)
Cystatin C equation	3.4 (2.3 to 4.4)	0.4 (−0.5 to 1.4)	6.0 (4.6 to 8.5)	8.5 (6.5 to 11.2)
Creatinine–cystatin C equation	3.9 (3.2 to 4.5)	1.3 (0.5 to 1.8)	6.9 (5.0 to 8.9)	10.6 (9.5 to 12.7)
Average of creatinine and cystatin C†	3.5 (2.8 to 4.1)	0.4 (−0.3 to 0.8)	6.5 (4.6 to 8.4)	11.9 (9.9 to 13.9)
Precision — IQR of the difference (95% CI)				
Creatinine equation	15.4 (14.3 to 16.5)	10.0 (8.9 to 11.0)	19.6 (17.3 to 23.2)	25.0 (21.6 to 28.1)
Cystatin C equation	16.4 (14.8 to 17.8)	11.0 (10.0 to 12.4)	19.6 (16.1 to 23.1)	22.6 (18.8 to 26.3)
Creatinine–cystatin C equation	13.4 (12.3 to 14.5)	8.1 (7.3 to 9.1)	15.9 (13.9 to 18.1)	18.8 (16.8 to 22.5)
Average of creatinine and cystatin C equations†	13.9 (12.9 to 14.7)	7.9 (7.1 to 9.0)	15.8 (13.9 to 17.7)	18.6 (16.1 to 22.2)
Accuracy — % (95% CI)‡				
$1 - P_{30}$				
Creatinine equation	12.8 (10.9 to 14.7)	16.6 (13.6 to 19.7)	10.2 (6.4 to 14.2)	7.8 (5.1 to 11.0)
Cystatin C equation	14.1 (12.2 to 16.2)	21.4 (18.2 to 24.9)	12.7 (8.5 to 17.4)	2.2 (0.6 to 3.9)
Creatinine–cystatin C equation	8.5 (7.0 to 10.2)	13.3 (10.7 to 16.1)	5.3 (2.7 to 8.2)	2.3 (0.9 to 4.2)
Average of creatinine and cystatin C equations†	8.2 (6.7 to 9.9)	12.1 (9.5 to 14.8)	6.4 (3.6 to 9.7)	2.9 (1.3 to 4.9)
$1 - P_{20}$				
Creatinine equation	32.9 (30.1 to 35.7)	37.2 (33.1 to 41.2)	31.1 (25.1 to 37.4)	26.5 (21.7 to 31.4)
Cystatin C equation	33.0 (30.3 to 35.7)	42.1 (38.2 to 46.1)	29.3 (23.6 to 35.4)	19.4 (15.4 to 23.7)
Creatinine–cystatin C equation	22.8 (20.4 to 25.2)	28.6 (25.1 to 32.4)	17.8 (13.3 to 22.9)	16.2 (12.4 to 20.5)
Average of creatinine and cystatin C equations†	23.7 (21.3 to 26.1)	29.1 (25.7 to 32.8)	17.6 (13.2 to 22.4)	18.8 (14.6 to 23.2)

BIS2: $767 \times \text{cystatin C}^{-0.61} \times \text{creatinine}^{-0.40} \times \text{age}^{-0.57} \times 0.87$ (if female)

$$\text{eGFR} = 130 \times \text{cystatin C}^{-1.069} \times \text{age}^{-0.117} - 7$$ CAPA

$$\text{FAS}_{\text{cysC}} = \frac{107.3}{\frac{\text{ScysC}}{\text{Q}_{\text{cysC}}}} \times \left[0.988^{(\text{Age}-40)} \text{ when age} > 40 \text{ years}\right].$$

$$\text{FAS}_{\text{combi}} = \frac{107.3}{\alpha \times \frac{\text{Scr}}{\text{Q}_{\text{crea}}} + (1-\alpha) \times \frac{\text{ScysC}}{\text{Q}_{\text{cysC}}}} \times \left[0.988^{(\text{Age}-40)} \text{ when age} > 40 \text{ years}\right].$$

Cystatine C

- + Combinée
- “Cost-effectiveness?”
- Une certaine imprécision reste au niveau individuel

Cystatine C en pédiatrie

- Valeurs de référence identiques de 2 à 50 ans
- Schwartz (CKiD) (n=643, n=322) (PENIA)

$$eGFR = 70.69 \times [\text{cystatin C (mg/L)}]^{-0.931}$$

$$eGFR = 39.8 \times [\text{height (m)}/S_{Cr}\ \text{(mg/dL)}]^{0.456} \times [1.8/\text{cystatin C (mg/L)}]^{0.418} \times [30/\text{BUN (mg/dL)}]^{0.079} \times [1.076]^{\text{gender}} \times [\text{height (m)}/1.4]^{0.179}$$

Références	Echantillon (n)	Mesure du DFG	CysC	Population	Formules
Bokenkamp [80]	83	inuline	PETIA	Pédiatrie	(162/CC)-30
Filler [120]	536	^{99}Tc-DTPA	PENIA	Pédiatrie	$91{,}62*(1/CC)^{1{,}123}$
Grubb [94]	536	Iohexol	PETIA	Divers + pédiatrie (n = 85)	$84{,}69*CC^{-1{,}68}*1{,}384$ si moins de 14 ans
Bouvet [87]	67	^{51}Cr-EDTA	PENIA	Pédiatrie	$63{,}2*(SCr/96)^{-0{,}35}*(CC/1{,}2)^{-0{,}56}*(poids/45)^{0{,}3}*(âge/14)^{0{,}4}$
Zappitelli [88]	103	Iothalamate	PENIA	Pédiatrie	1) $7594/(CC^{1{,}17})*1{,}2$ si greffé rénal 2) $(43{,}82*e^{0{,}003*taille})/(CC^{0{,}635}*SCr^{0{,}547})$

Chehade et al. [68]:

$$eGFR = 0.42 \times (Ht/Scr) - 0.04 \times (Ht/Scr)^2 - 14.5 \times CysC + 0.69 \times Age + (18.25 \text{ if female, or } 21.88 \text{ if male})$$

+CAPA
+FAS

Schwartz GJ, Kidney Int, 2012, 82, 445

Table 2 | Precision, goodness of fit, and agreement of eGFR derived from coefficients of indicated regression model; *N*=643 (i.e., 2/3 of 965) training set children-visits of the CKiD study

$eGFR = a\,(height/Scr)^b\,(1.8/Cystatin\ C)^c\,(30/BUN)^d\,(e^{male})\,(height/1.4)^f$

Model	*a*	*b*	*c*	*d*	*e*	*f*	$\sqrt{MSE}$	R^2	% of eGFR within 30% of iGFR	% of eGFR within 10% of iGFR
Univariate										
I: ht/SCr	42.3 ± 0.3	0.780 ± 0.016					0.184	78.5%	84.3	40.4
II: Cystatin C	40.9 ± 0.3		0.931 ± 0.020				0.190	77.1%	84.9	42.3
III: BUN	41.0 ± 0.5			0.613 ± 0.024			0.280	50.2%	67.8	26.1
Bivariate										
I and II	41.6 ± 0.3	0.443 ± 0.026	0.479 ± 0.031				0.157	84.3%	90.1	46.5
I and III	41.9 ± 0.3	0.662 ± 0.021		0.171 ± 0.021			0.175	80.6%	86.5	42.8
II and III	40.8 ± 0.3		0.796 ± 0.027	0.157 ± 0.022			0.183	78.7%	84.9	42.8
Multivariate										
I and II and III	41.5 ± 0.3	0.417 ± 0.026	0.431 ± 0.032	0.088 ± 0.019			0.155	84.8%	89.4	47.1
Final	39.8 ± 0.4	0.456 ± 0.026	0.418 ± 0.031	0.079 ± 0.018	1.076 ± 0.013	0.179 ± 0.032	0.147	86.3%	91.3	48.8

Abbreviations: BUN, blood urea nitrogen (mg/dl); CKiD, Chronic Kidney Disease in Children study; cystatin C (mg/l); eGFR, estimated glomerular filtration rate (ml/min per 1.73 m^2); height (m); iohexol GFR (ml/min per 1.73 m^2); MSE, mean square error; Scr, serum creatinine (mg/dl).
Entries for a–f are regression coefficient ± s.e.

Table 4 | Application of univariate cystatin C prediction equations to 1/3 validation set of 322 person-visits of the CKiD study with iGFR 44.4 ± 17.2 ml/min per 1.73 m^2

Equation	eGFR	Bias[a]	95% LOA[b]	Correlation	% of eGFR within 30% of iGFR	% of eGFR within 10% of iGFR
CKiD[c]	44.7 ± 15.2	0.3	−17.5, 18.1	0.85	82.6	37.6
Zappitelli *et al.*[21 d]	43.5 ± 18.7	−1.0	−20.5, 18.6	0.85	77.3	37.6
Filler and Lepage[4 e]	53.5 ± 21.9	9.0	−14.0, 32.0	0.85	64.3	21.7
Hoek *et al.*[22 f]	45.0 ± 18.0	0.6	−18.4, 19.6	0.85	78.6	37.9

Schwartz GJ, Kidney Int, 2012, 82, 445

FAS versus Schwartz

Table 6. Children $n = 368$ (age ≤ 18 years)

	Scr-based eGFR			ScysC-based eGFR			Combined Scr-/ScysC-based eGFR	
mGFR = 89.2 ($n = 368$)	FAS_{crea}	FAS_{crea}(Ht)*	$Schwartz_{crea}$	FAS_{cysC}*	CAPA	$Schwartz_{cysC}$	FAS_{combi}*	FAS_{combi}(Ht)*
eGFR − mGFR	12.3 (7.7; 17.0)	3.8 (0.9; 6.6)	11.1 (8.1; 14.1)	−5.1 (−7.2; −3.1)	**0.3** (−2.0; 2.6)	−21.6 (−23.7; −19.6)	**0.9** (−0.9; 2.7)	−2.2 (−4.0; −0.4)
eGFR/mGFR	1.17 (1.12; 1.21)	1.06 (1.04; 1.09)	1.15 (1.12; 1.18)	**0.98** (0.96; 1.01)	**1.03** (1.00; 1.05)	0.79 (0.78; 0.81)	1.05 (1.03; 1.07)	**1.01** (0.99; 1.03)
RMSE	47.0 (27.2; 67.6)	28.3 (11.4; 39.2)	31.3 (13.9; 42.9)	20.4 (17.9; 22.5)	22.3 (20.0; 24.3)	29.6 (27.0; 32.1)	**17.5** (15.1; 19.7)	**17.6** (15.5; 19.7)
Lin's CCC	0.43 (0.36; 0.49)	0.65 (0.59; 0.70)	0.63 (0.57; 0.68)	0.73 (0.68; 0.77)	0.74 (0.68; 0.78)	0.49 (0.44; 0.54)	**0.81** (0.77; 0.84)	**0.80** (0.77; 0.84)
P10 (%)	32.3 (27.5; 37.1)	42.7 (37.6; 47.7)	40.5 (35.5; 45.5)	40.5 (35.5; 45.5)	36.4 (31.5; 41.4)	16.0 (12.3; 19.8)	**44.6** (39.5; 49.7)	**43.2** (38.1; 48.3)
P30 (%)	78.3 (74.0; 82.5)	84.5 (80.8; 88.2)	79.9 (75.8; 84.0)	86.1 (82.6; 89.7)	76.6 (72.3; 81.0)	68.8 (64.4; 73.5)	**90.8** (87.8; 93.7)	**92.1** (89.4; 94.9)
mGFR <60 mL/min/1.73 m² ($n = 57$)								
mGFR = 45.2	FAS_{crea}	FAS_{crea}(Ht)*	$Schwartz_{crea}$	FAS_{cysC}	CAPA	$Schwartz_{cysC}$*	FAS_{combi}	FAS_{combi} (Ht)*
eGFR − mGFR	12.5 (10.0; 15.1)	5.1 (3.0; 7.2)	8.8 (6.5; 11.0)	6.2 (3.1; 9.3)	3.3 (−0.4; 7.1)	**−2.4** (−5.0; 0.2)	8.3 (6.2; 10.5)	5.0 (2.9; 7.1)
eGFR/mGFR	1.31 (1.24; 1.37)	1.14 (1.08; 1.20)	1.22 (1.16; 1.29)	1.17 (1.09; 1.25)	1.10 (1.01; 1.19)	**0.98** (0.91; 1.04)	1.21 (1.15; 1.27)	1.14 (1.08; 1.20)
RMSE	15.8 (12.7; 18.4)	9.4 (7.5; 10.9)	12.2 (9.7; 14.2)	13.1 (9.8; 15.7)	14.3 (10.4; 17.3)	**10.0** (7.5; 12.0)	11.6 (9.4; 13.5)	**9.3** (7.3; 11.0)
Lin's CCC	0.44 (0.29; 0.56)	**0.66** (0.50; 0.77)	0.55 (0.40; 0.68)	0.48 (0.29; 0.64)	0.47 (0.28; 0.63)	0.55 (0.35; 0.71)	0.56 (0.41; 0.69)	**0.65** (0.49; 0.77)
P10 (%)	10.5 (2.3; 18.7)	**45.6** (32.3; 58.9)	36.8 (23.9; 49.8)	24.6 (13.0; 36.1)	29.8 (17.6; 42.1)	36.8 (23.9; 49.8)	28.1 (16.0; 40.1)	38.6 (25.6; 51.6)
P30 (%)	63.2 (50.2; 76.1)	71.9 (59.9; 84.0)	71.9 (59.9; 84.0)	68.4 (56.0; 80.9)	66.7 (54.0; 79.3)	**86.0** (76.7; 95.3)	71.9 (59.9; 84.0)	80.7 (70.1; 91.3)
mGFR ≥60 mL/min/1.73 m² ($n = 311$)								
mGFR = 97.3	FAS_{crea}	FAS_{crea}(Ht)*	$Schwartz_{crea}$	FAS_{cysC}*	CAPA	$Schwartz_{cysC}$	FAS_{combi}*	FAS_{combi} (Ht)*
eGFR − mGFR	12.3 (6.8; 17.8)	3.5 (0.1; 6.9)	11.5 (8.0; 15.1)	−7.2 (−9.5; −5.0)	**−0.2** (−2.9; 2.4)	−25.2 (−27.4; −23.0)	**−0.5** (−2.5; 1.6)	−3.5 (−5.6; −1.4)
eGFR/mGFR	1.14 (1.09; 1.19)	1.05 (1.02; 1.08)	1.13 (1.10; 1.17)	0.95 (0.93; 0.97)	**1.02** (0.99; 1.04)	0.76 (0.74; 0.78)	**1.01** (0.99; 1.03)	**0.98** (0.96; 1.00)
RMSE	50.7 (10.5; 77.5)	30.5 (10.1; 42.0)	33.7 (12.7; 45.9)	21.5 (18.8; 23.8)	23.5 (21.0; 25.8)	32.0 (29.1; 34.5)	**18.4** (13.5; 20.8)	**18.8** (16.3; 21.0)
Lin's CCC	0.29 (0.22; 0.37)	0.50 (0.41; 0.57)	0.48 (0.40; 0.55)	0.59 (0.52; 0.65)	0.60 (0.52; 0.66)	0.33 (0.27; 0.38)	**0.71** (0.65; 0.76)	**0.69** (0.62; 0.74)
P10 (%)	36.3 (31.0; 41.7)	42.1 (36.6; 47.6)	41.2 (35.7; 46.7)	43.4 (37.9; 48.9)	37.6 (32.2; 43.0)	12.2 (8.6; 15.9)	**47.6** (42.0; 53.2)	44.1 (38.5; 49.6)
P30 (%)	81.0 (76.6; 85.4)	86.8 (83.0; 90.6)	81.4 (77.0; 85.7)	89.4 (85.9; 92.8)	78.5 (73.9; 83.1)	65.6 (60.3; 70.9)	**94.2** (91.6; 96.8)	**94.2** (91.6; 96.8)

Asterisks indicate the best performing equation(s) [13] within the same biomarker category, across all performance statistics. The bold values are the best result(s) for each performance statistic, across all equations. FAS, full-age-spectrum eGFR equation, based on Q(age); FAS(Ht), FAS equation based on Q(height); Schwartz, Schwartz equation for children (Scr-based = 0.413 Ht/Scr; cystatin C-based = 70.1 $ScysC^{-0.93}$). FAS_{combi} is calculated for $\alpha = 0.5$.

Pottel H, Nephrol Dial Transplant, 2017, 32, 497

Dernière publi de Schwartz

N=187
Après 18 ans (max 26 ans)

Table 2 | Measures of agreement for CKiD and CKD-EPI eGFR equations with iGFR as the reference for 279 person-visits contributed by 187 young adults with a history of pediatric CKD

Variable	iGFR	$CKiD_{SCr\text{-}Cys}$	$CKiD_{SCr}$	$CKD\text{-}EPI_{SCr}$	$CKD\text{-}EPI_{Cys}$	$CKD\text{-}EPI_{SCr\text{-}Cys}$
Mean, ml/min per 1.73 m^2	49.2	50.7	43.6	57.4	51.8	52.4
SD	22.5	21.1	20.2	30.8	29.4	29.2
Average bias, ml/min per 1.73 m^2 (95% CI)	0	**+1.5 (+0.6, +2.5)**	**-5.6 (-7.1, -4.2)**	**+8.2 (+6.7, +9.7)**	**+2.7 (+1.3, +4.0)**	**+3.3 (+2.1, +4.4)**
Ratio of SDs (95% CI)	1	**0.94 (0.89, 0.99)**	**0.89 (0.81, 0.97)**	**1.39 (1.28, 1.50)**	**1.32 (1.24, 1.40)**	**1.31 (1.24, 1.38)**
Correlation	1	0.94	0.89	0.91	0.90	0.94
RMSE, ml/min per 1.73 m^2	0	7.1	9.2	13.0	12.3	10.0
Percentage within 30% of iGFR	Reference	90	71	66	74	76

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology; $CKD\text{-}EPI_{Cys}$, CKD-EPI eGFR equation based on cystatin C only; $CKD\text{-}EPI_{SCr}$, CKD-EPI eGFR equation based on serum creatinine only; $CKD\text{-}EPI_{SCr\text{-}Cys}$, CKD-EPI eGFR equation based on serum creatinine and cystatin C; $CKiD_{SCr}$, CKiD eGFR equation based on serum creatinine only; $CKiD_{SCr\text{-}Cys}$, CKiD eGFR equation based on serum creatinine and cystatin C; eGFR, estimated glomerular filtration rate; iGFR, iohexol GFR; RMSE, root mean square error. Bold indicates statistically different from 0 for bias or statistically different from 1 for ratio of SDs ($P < 0.05$).

Schwartz GJ, Kidney Int, 2018

Cystatine C en pédiatrie

- Mêmes valeurs de référence que adultes
- Formule combinée de Schwartz: surtout CKD
- Formule avec Cystatine C non standardisée (PENIA)
- FAS (standardisée) et CAPA (standardisée)
- « Cost-effectiveness »?

Le sujet « âgé »


SI ON AVAIT SON ANNIVERSAIRE DEUX FOIS PAR AN
ON VIVRAIT DEUX FOIS PLUS VIEUX
© casterman - geluck

Comparaison des exactitudes à 30%
-CKD-EPI vs BIS

- *Koppe L et al. J Nephrol, 2013*
  - **n=224, Mean Age=75** 72% vs 76%
- *Lopes M et al. BMC Nephrology, 2013*
  - **n=95, Mean Age=85** 75% vs 80%
- *Alshoer I et al. AJKD, 2014*
  - **n=394, Median Age=80** 83% vs 88%
- *Vidal-Petiot E et al. AJKD, 2014*
  - **N=609, Mean Age=76** 82% vs 84%

Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals

Li Fan,[*†] Andrew S. Levey,[*] Vilmundur Gudnason,[‡§] Gudny Eiriksdottir,[‡] Margret B. Andresdottir,[‖] Hrefna Gudmundsdottir,[§‖] Olafur S. Indridason,[‖] Runolfur Palsson,[§‖] Gary Mitchell,[¶] and Lesley A. Inker[*]

J Am Soc Nephrol 26: 1982–1989, 2015.

N=805
+74 y

Equation	Bias Median Difference	Precision IQR	Accuracy P_{30}
eGFRcr			
CKD-EPI	−2.7 (−3.3 to −2.1)	12.1 (11.2 to 13.4)	91.7 (89.9 to 93.4)
Japanese	10.5 (9.8 to 11.2)[c]	10.9 (9.7 to 12.1)[a]	86.3 (83.9 to 88.6)[c]
BIS	5.7 (5.1 to 6.4)[c]	11.9 (10.6 to 12.7)[a]	95.8 (94.4 to 97.1)[b]

[a]No different than CKD-EPI.
[b]Better than CKD-EPI.
[c]Worse than CKD-EPI.

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ndt
Nephrology Dialysis Transplantation

Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort

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Table 2. Bias (median eGFR−mGFR, mL/min/1.73 m^2), precision (IQR, mL/min/1.73 m^2), absolute accuracy (median, percent) and P_{30} accuracy (percentage of GFR estimated within 30% of mGFR) of GFR estimating equations based on creatinine and the combination of creatinine and cystatin C in the AGES-Kidney cohort (*n* = 805)

Variables	LMR_{Cr}	FAS_{Cr}	$CKD\text{-}EPI_{Cr}$	$MEAN_{LMR+CAPA}$	FAS_{Cr+Cys}	$CKD\text{-}EPI_{Cr+Cys}$
Bias	−4.8 (−5.4 to − 4.2)[a]	−5.7 (−6.3 to − 5.1)[a]	2.7 (2.1 to 3.3)	−2.7 (−3.2 to − 2.1)[a]	−5.9 (−6.5 to − 5.4)[a]	0.6 (−0.1 to 1.2)
Precision	10.8 (10.1 to 11.5)[b]	10.7 (9.9 to 11.9)[b]	12.1 (11.2 to 13.4)	9.3 (8.5 to 10.1)[c]	10.0 (9.1 to 10.9)[c]	10.2 (9.0 to 11.1)
Absolute accuracy	11.4 (10.3 to 12.3)[c]	12.1 (11.1 to 13.2)[a]	10.2 (9.3 to 11.0)	8.5 (8.0 to 9.2)[c]	11.3 (10.5 to 12.3)[a]	8.1 (7.5 to 8.9)
P_{30} accuracy	95.0 (93.5 to 96.5)[b]	95.8 (94.4 to 97.2)[b]	91.7 (89.9 to 93.4)	97.3 (96.2 to 98.4)[b]	97.8 (96.7 to 98.8)[b]	96.1 (94.8 to 97.4)

Data are presented with 95% CIs.
[a]Significantly worse ($P < 0.05$) than corresponding CKD-EPI equation.
[b]Significantly better ($P < 0.05$) than corresponding CKD-EPI equation.
[c]No statistical difference ($P \geq 0.05$) compared with corresponding CKD-EPI equation.

AJKD

Correspondence

RESEARCH LETTER

Comparing Newer GFR Estimating Equations Using Creatinine and Cystatin C to the CKD-EPI Equations in Adults

Levey AS, Am J Kidney Dis, 2017, 70, 587

	CKD-EPI Validation (n=3896)	CKD-EPI Development (n=8254)
Age (years)	49.5 ± 14.7	47.0 ± 14.8
<18	0 (0%)	0 (0%)
18-39	1066 (27%)	2921 (35%)
40-65	2262 (58%)	4309 (52%)
>65	568 (15%)	1024 (12%)
Sex		
Male	2129 (55%)	4648 (56%)
Female	1767 (45%)	3606 (44%)
Race		
Non-African American	3512 (90%)	5653 (68%)
African American	384 (10%)	2601 (32%)
Measured GFR (ml/min/1.73m^2)	67.9 ± 35.8	67.6 ± 39.6
Geographic regions	North America Europe	North America Europe
GFR measurement method	Urinary clearance of iothalamate and EDTA, plasma	Urinary clearance of iothalamate

Equation	Bias Median Difference (mL/min/1.73 m^2)	Precision IQR of Differences (mL/min/1.73 m^2)	Accuracy 1 – P_{30} (%)	Accuracy RMSE
Performance of Creatinine Equations in Creatinine Validation Database (n=3,896)				
CKD-EPI	2.2 (1.8, 2.6)	16.6 (15.8, 17.2)	15.8 (14.7, 17.0)	0.249 (0.240, 0.259)
LMR	**7.4 (6.8, 7.8)**	**18.2 (17.6, 19.1)**	**20.3 (19.0, 21.6)**	**0.280 (0.272, 0.288)**
FAS	1.4 (1.0, 1.8)	**18.0 (17.3, 18.7)**	**18.3 (17.1, 19.5)**	0.261 (0.252, 0.271)
Performance of Cystatin C Equations in Cystatin C Validation Database (n=1,119)				
CKD-EPI	3.4 (2.3, 4.4)	16.4 (14.8, 17.7)	14.1 (12.1, 16.2)	0.234 (0.220, 0.250)
CAPA	3.8 (2.7, 4.9)	18.2 (16.6, 19.6)	16.3 (14.1, 18.4)	0.247 (0.233, 0.264)
FAS	**0.2 (–0.8, 1.4)**	**20.5 (18.6, 21.6)**	**23.9 (21.4, 26.5)**	**0.288 (0.270, 0.310)**

Limitations des formules = créatinine

Populations spécifiques:
Les équations ne sont pas magiques!!
Gardons notre sens clinique!!

Anorexie nerveuse (Delanaye P, Clin Nephrol, 2009, 71, 482)

Cirrhose (Skluzacek PA, Am J Kidney Dis, 2003, 42, 1169)

USI (Delanaye P, BMC Nephrology, 2014, 15, 9)

Hospitalisés (Poggio ED, Am J Kidney Dis, 2005, 46, 242)

Greffés cœur (Delanaye P, Clin Transplant, 2006, 20, 596)

Greffés rein (Masson I, Transplantation, 2013, 95, 1211)

Obèse (Bouquegneau A, NDT, 2013, 28, iv122)

Conclusions en pédiatrie

- Créatinine enzymatique à recommander
- Schwartz ou Schwartz-Lyon est une bonne équation (surtout CKD)
- FAS pas mal (taille), surtout si pas CKD
- Résultat « automatique » (screening)
- Cystatine C a une valeur ajoutée (combinée)
- DFG mesuré garde une place

Conclusions: formules un message double? un double message ?

- Pour les non-néphrologues:
  MDRD (ou CKD-EPI ou FAS) sont les moyens les plus simples pour estimer le DFG

- Pour les néphrologues:
  MDRD (ou CKD-EPI ou FAS) ne sont pas magiques, elles ont toutes des limitations à connaître

REVIEWS

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

Aujourd’hui, la question n’est pas tant de savoir quelle équation est la meilleure mais quand un recours au DFG mesuré est pertinent

Delanaye P, Nature Rev Nephrol, 2013, 9, 513

Nephrol Dial Transplant (2018) 1–8
doi: 10.1093/ndt/gfy086

CKD staging with cystatin C or creatinine-based formulas: flipping the coin

Sergio Luis-Lima[1], Beatriz Escamilla-Cabrera[2], Natalia Negrín-Mena[1], Sara Estupiñán[2], Patricia Delgado-Mallén[2], Domingo Marrero-Miranda[2], Ana González-Rinne[2], Rosa Miquel-Rodríguez[2], María Ángeles Cobo-Caso[2], Manuel Hernández-Guerra[3], Juana Oramas[4], Norberto Batista[4], Ana Aldea-Perona[1], Pablo Jorge-Pérez[5], Carlos González-Alayón[3], Miguel Moreno-Sanfiel[3], Juan Antonio González-Rodríguez[6], Laura Henríquez[7], Raquel Alonso-Pescoso[7], Laura Díaz-Martín[1], Federico González-Rinne[1], Bernardo Alio Lavín-Gómez[8], Judith Galindo-Hernández[7], Macarena Sánchez-Gallego[7], Alejandra González-Delgado[9], Alejandro Jiménez-Sosa[1], Armando Torres[2,10] and Esteban Porrini[10]

- N=882, iohexol
- 61 équations, habilité de chaque à classer en stade 1,2,3,4,5
- Erreur de classification

    Cystatine C: 35%, créatinine: 50%

- Comment estimer?

- Comment mesurer?

- Comment estimer?
- Comment mesurer?

Mesure le DFG: Pourquoi? Question de précision!

- Décision de démarrer la dialyse
- Sarcopénie
- Taille/poids extrêmes
- Cirrhose, Hyperfiltration
- Pédiatrie (=> ci-dessus)
- Don de rein vivant
- Médicaments néphrotoxiques (=> + ci-dessus)
- Recherche clinique, EMA
- Pas de preuve définitive…

Mesurer le DFG: Comment

- Clairances urinaires

- Clairances plasmatiques

Urines versus plasma pro-con

- Plus physiologique
- Plus couteux
- Plus difficile
- Différences sont systématiques

Plasma: échantillons multiples ou uniques

Nephrol Dial Transplant (2018) 1–8
doi: 10.1093/ndt/gfx345

Single- versus multiple-sample method to measure glomerular filtration rate

Pierre Delanaye[1,*], Martin Flamant[2,*], Laurence Dubourg[3,4], Emmanuelle Vidal-Petiot[2], Sandrine Lemoine[3], Etienne Cavalier[5], Elke Schaeffner[6], Natalie Ebert[6,**] and Hans Pottel[7,**]

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Marqueurs…

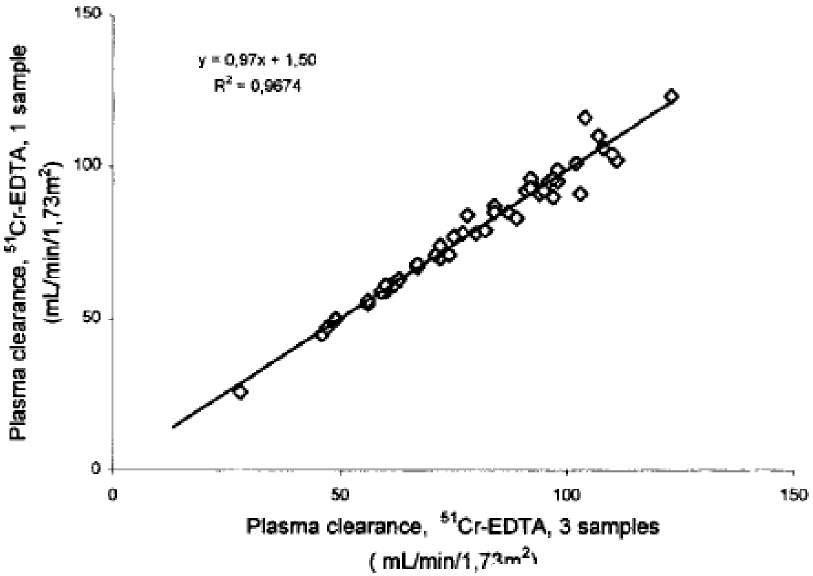
Marqueurs	Forces	Limitations
Inuline	Gold standard (ou historique) Était “safe”…	Couteux Dosage non standardisé Doute avec clairances plasmatiques simplifiées
Iothalamate	Le + populaire aux USA Méthde isotopique ou “froide”	Sécrétion Tubulaire Allergie à l’iode
Iohexol	Le + populaire en Europe Méthode froide	Worldwide available Allergie à l’iode
EDTA	Facile à mesurer	Isotopique Pas disponible aux USA
DTPA	Facile à mesurer	Isotopique Liaison aux protéines Demi-vie courte

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
Sovori I, AJKD, 2014, 64, 411
Delanaye P, Clin Kidney J, 2016, 9, 700

Equivalent?

EDTA versus iohexol

N=49



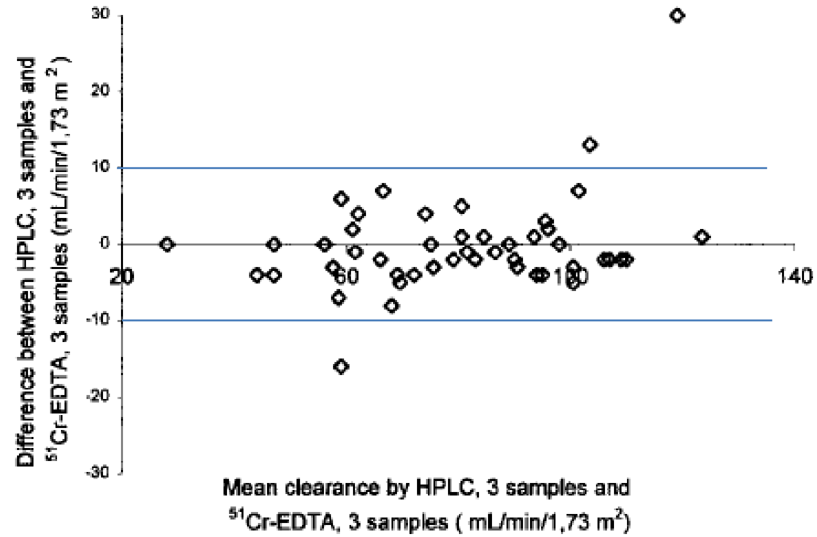


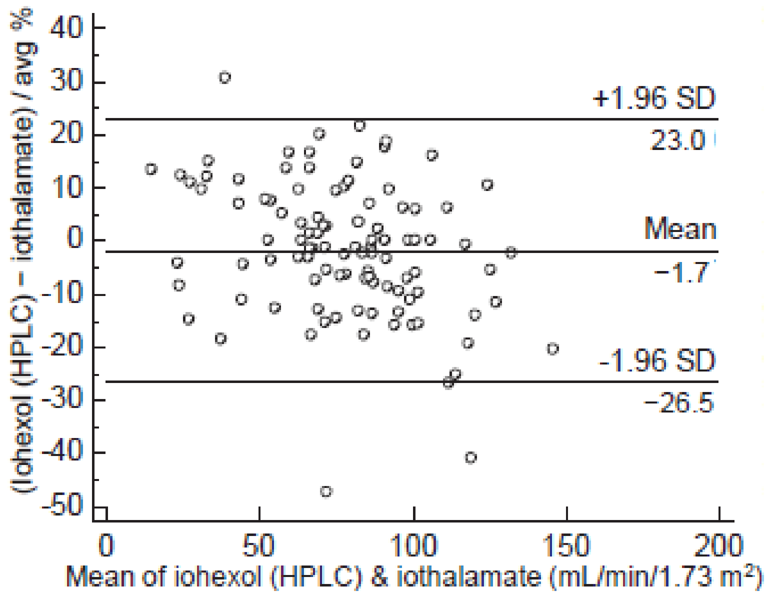
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	Clearance range (ml/min)	Difference (ml/min)	
		Mean	SD
Multiple-point clearance: 3 samples ^{51}Cr-EDTA *vs* 3 samples iohexol			
^{51}Cr-EDTA *vs* HPLC	28–134	−0.16	6.17
^{51}Cr-EDTA *vs* X-ray fluorescence	29–134	0.58	4.95
Single-point clearance: 3 samples ^{51}Cr-EDTA *vs* 1 sample			
^{51}Cr-EDTA *vs* ^{51}Cr-EDTA	26–123	−0.7	3.59
^{51}Cr-EDTA *vs* HPLC	27–125	−1.7	5.94
^{51}Cr-EDTA *vs* X-ray fluorescence	32–116	−1.32	5.78

Brandstrom E, NDT, 1998, 13, 1176

Iothalamate versus iohexol

N=102



Accuracy (concordance):
Within 30%: 98%
Within 15%: 80%

Delanaye, AJKD, 2016, 68, 329

Amélioration…
1) Standardisation de la procédure

- Urine versus plasma
- Nombre d'échantillons, timing
- Quelque soit le marqueur…

Table 4. Available procedures to perform iohexol clearance

Methodology	Indication in clinical practice	Indication in clinical research	Bibliographic examples where the procedure is described into details
Urinary clearance	Increased extracellular volume (oedema, ascites, intensive care units, etc.)	Basic (physiologic) studies Specific populations (cirrhotic, intensive care, nephrotic syndrome, oedema, etc.)	[36, 77, 125, 170]
Plasma clearance			
Multiple samples (first or fast, second or slow exponential curves and calculation of area under the curve)	High GFR values ('hyperfiltrating') subjects	Development of equations to estimate GFR Studies in hyperfiltrating patients	[52, 93, 171]
Multiple samples only for second and slow component (2 h after injection, 4 samples over 5 or 6 h, 1 sample/h) + BM correction	High precision determination (see text)	Development of equations to estimate GFR Clinical research with GFR as main endpoint	[126, 172]
Idem + late sample (8 h or 24 h)	Pre-dialysis subjects	Research in pre-dialysis subjects	[52, 77]
Simplified two or three sample method (2 samples: first at 2 or 3 h and second at 4 or 5 h) + BM correction	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint	[69, 116]
Simplified single-sample method + Jacobsson correction [110]	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint Epidemiological research	[14, 173]

Suggestions (expert opinion-based) according to the clinical or experimental context.
GFR, glomerular filtration rate; CKD, chronic kidney disease; BM, Brochner-Mortensen correction [116].

Delanaye P, Clin Kidney J, 2016, 9, 700

Standardisation du marqueur

- Seuls les méthodes froides sont facilement implémentées partout dans le monde
- Iothalamate difficile à obtenir en Europe
- Inuline: vous savez…
- Iohexol est disponible partout
- Très stable (laboratoire central)
- Contrôle externe existe (Equalis, Suède)

Delanaye P, Clin Kidney J, 2016, 9, 700
Delanaye P, Clin Kidney J, 2016, 9, 682

Conclusions

- Mesurer le DFG n'est pas si difficile (et pas si cher)
- Standardisation peut/doit encore être améliorée
- Iohexol est le meilleur rapport entre physiologie et faisabilité
- Iohexol est sans danger **(Gaspari F, Nephron, 2018)**
- Iohexol est la seule chance d'avoir un jour une méthode de référence standardisée qui serait la même partout dans le monde

Merci de votre attention!